Unifying the DNA end-processing roles of the artemis nuclease: Ku-dependent artemis resection at blunt DNA ends.

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Public Summary:
We were able to explain what parts of the DNA that the nuclease, Artemis, recognizes to carry out its important functions in the human immune system and in the repair of double-strand DNA breaks that arise due to normal aspects of our natural environment (oxygen in the air and natural background radiation from the metals in the earth and the radiation from outside space).

Scientific Abstract:
Artemis is a member of the metallo-beta-lactamase protein family of nucleases. It is essential in vertebrates because, during V(D)J recombination, the RAG complex generates hairpins when it creates the double strand breaks at V, D, and J segments, and Artemis is required to open the hairpins so that they can be joined. Artemis is a diverse endo- and exonuclease, and creating a unified model for its wide range of nuclease properties has been challenging. Here we show that Artemis resects iteratively into blunt DNA ends with an efficiency that reflects the AT-richness of the DNA end. GC-rich ends are not cut by Artemis alone because of a requirement for DNA end breathing (and confirmed using fixed pseudo-Y structures). All DNA ends are cut when both the DNA-dependent protein kinase catalytic subunit and Ku accompany Artemis but not when Ku is omitted. These are the first biochemical data demonstrating a Ku dependence of Artemis action on DNA ends of any configuration. The action of Artemis at blunt DNA ends is slower than at overhangs, consistent with a requirement for a slow DNA end breathing step preceding the cut. The AT sequence dependence, the order of strand cutting, the length of the cuts, and the Ku-dependence of Artemis action at blunt ends can be reconciled with the other nucleolytic properties of both Artemis and Artemis.DNA-PKcs in a model incorporating DNA end breathing of blunt ends to form transient single to double strand boundaries that have structural similarities to hairpins and fixed 5' and 3' overhangs.